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Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Comments on FDA Guidance for Industry: Botanical Drug Products
Docket No. 00D-1392

Enclosed (in duplicate) are Ancile Pharmaceutical's comments on the draft Guidance for Industry for Botanical Drug Products, in response to the Federal Register Notice, published August 11, 2000.

Sincerely,

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COMMENTS ON
FDA GUIDANCE FOR INDUSTRY: BOTANICAL DRUG PRODUCTS
Announced in Federal Register Vol. 65, No. 156, p. 49247, August 11, 2000
Docket No. 00D-1392

1.0 GENERAL COMMENTS ON GUIDANCE DOCUMENT

1.1 Agreement with Guidance, in principle

Ancile Pharmaceuticals (hereafter referred to as Ancile) embraces the guidance document, in principle. Ancile welcomes the issuance of the guidance document for the development and approval of botanical drug products. This guidance provides useful information on the overall development of botanicals as drug products. The document should help validate FDA's willingness to approve botanicals as prescription or OTC drugs, provided that data generated in accord with the recommendations of, and under the auspices of, the guidance document justifies such action. The guidance should also encourage consistency in requirements and recommendations among the various Reviewing Divisions within the Center for Drug Evaluation and Research for the development and approval of botanical drug products.

1.2 Current FDA/ICH Chemistry Guidelines *vis a vis* Guideline for Botanical Drug Products

Clarification is needed that, for botanical drug products, the principles set forth in the "Guidance for Industry: Botanical Drug Products" will supersede any principles set forth in guidance documents for non-botanical products, if such the principles differ or represent conflicting guidance. Clarification is also needed as to

the application of current FDA chemistry guidelines to botanical drug products. Will current chemistry guidelines be amended to reflect the guideline for Botanical Drug Products? Examples of guidance documents that may include recommendations that differ from the "Guidance for Industry: Botanical Drug Products" are:

Format and Content of the Chemistry, Manufacturing and Controls Section of an Application
Draft ICH Consensus Guideline on Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (***See section 4.3 of these comments for a specific example.)***
Format and Content for the CMC Section of an Annual Report
Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products
Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances
Analytical Procedures and Methods Validation (draft)
INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Product Chemistry, Manufacturing and Controls Content and Format
Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products
Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances
Drug Master Files

1.3 Need for additional, more specific guidelines

FDA has issued very specific guidelines for the chemistry, manufacturing and controls of drug substances produced by synthesis, fermentation, purification, etc. Clarification is needed if the "Guidance for Industry: Botanical Drug Products" will eventually be augmented with guidance documents that provide more detailed information on the development of botanical drugs and the CMC section of NDAs for botanical drug products. Will further guidance documents that cover more detailed topics [such as analytical procedures, methods validation, impurities in drug substances, submitting supporting documentation in drug applications for the manufacture of botanical drug products, dissolution, post-approval changes to approved botanical NDAs, and waivers for bioavailability data], analogous to the current guidelines for new chemical entities, be issued for botanical drug products?

1.4 Query: FDA's enforcement policy *vis a vis* dietary supplements

Ancile is certainly not suggesting that a response to the following query be included in the guidance document *per se*. However, in our opinion, clarification is needed as to what the FDA's enforcement policy will be, if during the course of development of a botanical, a company provides the agency with information that would indicate a public health safety issue for botanicals currently marketed as foods (under DSHEA or as medical foods), e.g. –

- carcinogenicity (*vis a vis* the Delaney Amendment)
- teratogenicity
- drug abuse liability potential
- serious adverse events.

Given that the current labeling for food products does not accommodate the communication of such safety information to the consumer for products regulated as foods, will FDA remove from the marketplace botanical products marketed as foods that represent a potential public health safety issue, based on data generated under an IND?

The following comments apply to specific issues addressed in the guidance document:

2.0 GENERAL REGULATORY APPROACHES / POLICIES

2.1 Acceptability of OTC Monographs for Certain Botanical Drug Products

page 3, A. Marketing Under OTC Monograph Versus Approved NDA; 1st ¶

"A botanical product that has been marketed in the United States for a material time and to a material extent for a specific OTC drug indication may be eligible for inclusion in an OTC monograph codified in 21 CFR Parts 331-338. The manufacturer would need to submit a petition to amend the monograph to add the botanical substance as a new active ingredient in accordance with 21 CFR 10.30."

Clarification is needed that the same standards for the evaluation of safety and efficacy will be applied to OTC monograph petitions for botanical drug products as will be applied for the approval of a botanical product New Drug Application. For example, Echinacea is currently marketed as a dietary supplement with the structure/function claim that "it stimulates the body's own defenses". Requirements for approval of an NDA for Echinacea would include a full ICH-compliant toxicology program, as well as demonstration of efficacy, based on adequate and well-controlled clinical trials to demonstrate efficacy. The clinical safety studies would need to include thousands of patients, dosed for the duration required by ICH guidelines. Please verify that FDA would impose the same data requirements for an OTC cough/cold monograph petition, as would be required for approval of an NDA for the OTC marketing of Echinacea for the symptomatic relief of coughs and colds. Other examples of products currently marketed as dietary supplements include Kava Kava, Valerian, Ginseng, St. John's Wort, Saw Palmetto, etc., for which full ICH- and FDA drug development requirements apply for the approval of an NDA for such products. Will the agency apply the same development and approval standards for OTC monographs as are being applied for the approval of NDAs for botanical drug products?

2.2 Acceptability of ANDAs for Botanical Drug Products

page 3, footnote 4

"An applicant may submit an ANDA for a botanical drug product that is the same drug for the same indication as a previously approved drug product. The *generic* version of the previously approved drug would have to be both pharmaceutically equivalent and bio-equivalent to such drug."

Clarification is needed as to what standards will be used to determine the pharmaceutical and bioequivalency of a generic version of a botanical drug to one that is the subject of an approved NDA. The guidance does not require pharmacokinetic studies (page 16), if infeasible, for a botanical NDA. The guideline states that:

> "In some cases, a product's active moieties may not be known, and standard pharmacokinetic measurements to demonstrate systemic exposure to a product in animals and/or humans may be infeasible. However, when feasible a sponsor should attempt to monitor the blood levels of known active ingredients,

representative markers, or major chemical constituents in a botanical drug product."

In addition, traditional bioequivalency studies probably will not measure all potential active constituents of a botanical drug product. Therefore, what standards will be applied for the demonstration of bioequivalency of a generic version of a botanical drug product previously approved under section 505 of the Act? The acceptance of ANDAs for botanical products appears to be inconsistent with the stipulations delineated in the guidance document. In addition, what criteria will the agency use to determine the pharmaceutical equivalency of a generic version to that of the originally NDA-approved botanical drug?

2.3 Market Exclusivity

page 4, 1st paragraph

"In contrast, when a product is approved under an NDA, the approval is specific to the drug product that is the subject of the application (the applicant's drug product), and the applicant may be eligible for marketing exclusivity for either 5 years (if it is a new chemical entity) or 3 years from the time of approval, even in the absence of patent protection."

Given that the requirements for approval of an NDA for a botanical drug product will be the same as for a new chemical entity (full nonclinical toxicology program, full clinical program, and equivalent chemistry, manufacturing, and controls), clarification is needed if a botanical drug product, approved under 505 (b) (1) of the Act, will be granted the same exclusivity as a "new chemical entity" (i.e., 5 years).

2.4 Exemption from Combination Drug Policy

page 5, ¶ 2

"Botanical drugs composed of multiple parts of a single plant species, or of parts from different plant species, currently are subject to the combination drug requirements. However, FDA intends to propose revisions to its regulations to allow for the exemption of such botanical drugs from application of the combination drug requirements under certain circumstances."

Clarification of "under certain circumstances" is needed. Will botanical drug products, composed of parts of multiple plants (e.g., Traditional Chinese Medicines), each included for the treatment of individual symptoms of a multi-symptom disease (e.g., irritable bowel syndrome), be exempt from the combination drug policy requirements? In addition to products used for multi-symptom diseases, will a product composed of parts of multiple plants, that are traditionally used in combination for the treatment of a homogeneous disease state, i.e. one major symptom, be exempt from the combination drug policy requirements?

3.0 CLINICAL

3.1 Use of Active Controls in Clinical Studies for Botanical Drug Products

VI. INDs For Botanical Drugs
B. Basic Format for INDs
5. Protocol

page 8, 2nd ¶

"For most conditions potentially treated by botanical drugs (generally mildly symptomatic), active control equivalence designs would not be credible."

We assume that an active control arm, in addition to a placebo control arm, would be acceptable in certain circumstances, if discussed with the Reviewing Division (e.g., during an end-of-Phase 2 meeting), prior to initiation of the clinical study. We also assume that an active control arm (with no placebo control) would be acceptable for disease states in which it would be unethical to use a placebo-controlled designed clinical trial, as is the case for new chemical entities. While this will not usually be the case for botanical drug products, botanical drug products may be developed in the future for disease states for which the same principles for clinical trial design would apply as for new chemical entities.

3.2 Dosage Forms for Clinical Studies for Certain Botanical Drug Products

VI. INDs For Botanical Drugs
B. Basic Format for INDs
6. Chemistry, Manufacturing, and Controls

page 10, 2nd full ¶

"Botanical raw materials may sometimes be dispensed at clinics on an *as needed* or *by prescription* basis and subsequently prepared by patients themselves at home. These practices should be avoided during clinical trials if at all possible because data related to such use may not be reliable due to variability of preparation among patients. When absolutely necessary, dispensing in such a manner may be considered for initial clinical studies. But as clinical trials are expanded, the botanical drug product should be produced in a controlled manner by an established manufacturer to ensure validity and reliability of data."

For some botanical drug products (particularly Traditional Chinese Medicines) the only dosage form may be a tea-like preparation. The tea bag (or similar dosage form) would be produced in a controlled manner by an established manufacturer. The patient would "dissolve" the tea-like preparation in water, for example, for dosing administration. Directions for administration would include a defined amount of water, the temperature of the water, and the seeping time. Clarification is needed as to whether this type of dosage form would be acceptable. We interpret the current language of the guidance document to imply that such a dosage form/delivery system would not be acceptable. Please clarify.

4.0 CHEMISTRY, MANUFACTURING AND CONTROLS

4.1 Quality control tests

4.1.1 Botanical Raw Material – Phase 3 Clinical Studies

IX. INDs for Phase 3 Clinical Studies of all Botanical Products
B. Chemistry, Manufacturing, and Controls
1. Expanded clinical studies
a. Botanical raw material

page 25; 1st bullet under subsection a

- **Voucher specimen**

"A voucher specimen of the plant or plant parts should be retained for every batch."

The definition of the term "voucher specimen" needs to be clarified. The following scenario represents a typical practice in cultivating plants, under Good Agricultural Practices:

1. The sponsor purchases seeds from a commercial grower and the contract grower uses these seeds for cultivation of the botanical.
2. The seeds from harvest F_1 are used to cultivate plants for harvest $F_2 \rightarrow F_{4,\ etc.}$ A **voucher specimen** of the plants used to produce the seeds for harvest $F_2 \rightarrow F_{4\ (etc.)}$ is maintained by the sponsor.
3. The sponsor maintains **retain samples** of each batch of harvested plant parts (roots, leaves, bark, etc.) (Botanical Raw Material), which are then extracted to produce the Botanical Drug Substance.

Does the term "voucher specimen", as used in the guideline, actually refer to "retain samples" for every batch of harvested Botanical Raw Material? What would be considered to be a "voucher specimen" for plants cultivated from cuttings? In summary, clarification is needed as to the use of the term "voucher specimen" in the guideline.

4.1.2 Botanical Drug Substance – Phase 3 Clinical Studies

IX. INDs for Phase 3 Clinical Studies of all Botanical Products
B. Chemistry, Manufacturing, and Controls
1. Expanded Clinical Studies
b. Botanical drug substance
- The *quality control* tests

page 27

- **Biological assay**

Clarification is needed regarding the blanket requirement for a biological assay for the Botanical Drug Substance (BDS) for Phase 3 clinical studies. If the chemical composition of a BDS is fully characterized, including identification of the active constituents, (> 90% w/w) and controlled from batch to batch, would FDA still require a biological assay for Quality Control release of the BDS?

Also, will a bioassay be required if the active ingredients are defined? If the active components are well defined and there is a direct correlation between the concentration of the active components and the activity of the botanical drug substance in a bioassay, would a bioassay still be required for lot-to-lot release of the Botanical Drug Substance?

Biological assays are inherently variable in nature (10 to 20%, depending on the assay). Thus, clarification is needed as to the range of variability that FDA will accept for biological assays used for QC release of the Botanical Drug Substance.

page 27

- **Animal safety test, if applicable**

Clarification is needed as to what animal safety tests would be needed for release of a Botanical Drug Substance. Would this apply only to injectable Botanical Drug Products (e.g., rabbit pyrogenicity testing)? Animal safety testing (e.g., rabbit pyrogenicity testing) is not routinely performed for quality control release of synthetic drugs. Each lot of Botanical Drug Substance (for Phase 3 clinical trials and commercial use) will be fully characterized for pesticide and toxin contamination and microbial

burden. It is unclear as to what is meant by animal safety tests and what they would contribute to the quality control of the Botanical Drug Substance.

4.1.3 Botanical Drug Product – Phase 3 Clinical Studies

IX. INDs for Phase 3 Clinical Studies of all Botanical Products
B. Chemistry, Manufacturing, and Controls
1. Expanded clinical studies
c. Botanical drug product
- The *quality control* tests

- **Chemical identification**

page 28 (last bullet) and page 29 (first bullet)

" The quality control tests, including, but not limited to, the following specifications:

- **Chemical identification by spectroscopic or chromatographic fingerprints**
- **Chemical identification for the active constituents or, if unknown, the characteristic markers"**

Clarification is needed regarding the last sentence of page 28 and the first sentence on page 29. What is the difference between the two chemical identification tests? And why are two identification tests required for the release of Botanical Drug Products? Typically one identification test is sufficient to release synthetic drug products. Because the drug substance (extract) will be well characterized, it is our opinion that one identity test for the Botanical Drug Product should be sufficient. The identity test should provide an easy method to confirm the identity of the drug product, for example chemical identification for the active ingredient or characteristic markers. A fingerprint is very complicated and would not provide any additional benefit over the simpler chemical identification using an active ingredient or characteristic marker. We recommend elimination of the dual identity tests by eliminating the fingerprint requirement.

- ***Biological Assay for Botanical Drug Product***

page 29; 3rd bullet

Why is a biological assay needed for the quality control of the Botanical Drug Product (BDP), if it is employed for the QC release of the Botanical Drug Substance (page 26) used for formulating the BDP? Strength and content uniformity of the BDP should be defined by "Weight" and "Content of Biological/Characteristic Markers".

- ***Adventitious toxins for Botanical Drug Product***

page 29, 7th bullet

"Adventitious toxins (e.g. aflatoxins)"

Why are tests for adventitious toxins needed for the drug product, when they are conducted for the Botanical Raw Material (page 26) and the Botanical Drug Substance (page 27)? Would it be adequate to demonstrate that if adventitious toxins are tested for (in compliance with cGMP standards) and are absent in the Botanical Raw Material and Botanical Drug Substance, that there is no possibility that they would be introduced during the manufacturing of the drug product?

4.1.4 Botanical Drug Products – NDA Considerations

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
B. Chemistry, Manufacturing, and Controls
2. End-of-Phase 3 Clinical Studies and Pre-NDA Considerations

- ***Chromatographic fingerprinting***

Fingerprints are referred to on several pages of the Botanical Guideline, including p 19 ¶ e (chemical identification – botanical drug substance); page 21 ¶ e (chemical identification – botanical drug product); page 25 and 26 second bullet points (quality control for botanical raw material); page 26 ¶ b (chemical identification – botanical drug substance); page 28 (chemical identification – botanical drug product); page 30 ¶ c; and page 36 - chromatographic fingerprint definition.

There appears to be inconsistency in the guideline. Chromatographic fingerprint is defined on page 36 as –

> "a chromatographic profile of a botanical raw material or drug substance that is matched qualitatively and quantitatively against that of a reference sample or standard to ensure the identity and quality of a batch and consistency from batch to batch."

The definition does not appear to apply to the botanical drug product. However, the guideline recommends that a chromatographic fingerprint be employed as a quality control test for the botanical drug product (pages 21, 28, 30).

The guideline defines several requirements relating to fingerprints for NDA approval. We would like to comment on two of those requirements:

page 30, ¶ c

c. Batch-to-batch consistency

"... All chemical constituents present in the drug substance batches should be qualitatively and quantitatively comparable based on spectroscopic and/or chromatographic fingerprinting."

Qualitatively concluding that one lot is consistent with another lot using a chemical fingerprint is too subjective to be useful, given the complexity of some botanical products, and the inherent variability in botanical products and analytical methods. Additionally, botanical constituents can range from low molecular weight lipophilic compounds to very polar high molecular weight constituents. Such range of compounds would require multiple fingerprints, which in turn would require complex comparisons that would not be practical, qualitatively.

Quantitative comparison of fingerprints requires very sophisticated data management and mathematical capabilities. Quantitative comparisons will require specifications. How these specifications will be established for complex fingerprints is not a straightforward issue. Fingerprints can be comprised of dozens of peaks that will each vary due to analytical methodology and the nature of botanical products. Determining pass/fail for this complex system will be challenging and possibly not feasible.

The fingerprint requirement should be made more flexible and less rigorous, in our opinion. The entire CMC package (strict quality

controls of the Botanical Raw Material, process validation, analytical methods, specifications, in-process controls, etc), submitted by the applicant, should be evaluated for product control and a specific fingerprint requirement should not be defined unless no other avenue is possible for adequate control of the product. This should be determined on a case-by-case basis.

page 30, ¶ e

e. Mass balance of the test sample

"... Analytical methods used for fingerprinting should be capable of detecting as many chemical constituents as possible. Multiple fingerprints, using a combination of analytical methods with different separation principles and test conditions, may be useful. Additionally, the analytical methods in combination should be able to demonstrate the mass balance of the test sample."

Using multiple fingerprints to determine a mass balance for an extract would require identification of all constituents, production of reference standards for each constituent and management of extensive data generated by these fingerprints. Because of the constituent variability inherent in botanical extracts and the complexity of the mixture, it is our opinion that employing fingerprints for mass balance calculations would not provide useful control for many of the more complex botanical products. We suggest more flexibility in this requirement by allowing classes of compounds to be determined quantitatively and used to establish a mass balance. For example, methods exist to routinely quantitate total fatty acids, total carbohydrates, etc. Although these methods can quantitate individual constituents from each class of compounds, little would be gained from this type of fingerprint information. We propose to use totals for classes of compounds as the basis for the mass balance. Additional mass balance components could include individual active constituents, major inactive metabolites and other prevalent compounds. This list would change depending on the nature of the botanical material but the goal would be to establish a mass balance accounting for all significant components. This would serve to chemically characterize the extract and allow for determination of lot-to-lot performance, reflected in the specification ranges for the extract constituents.

4.2 Stability-indicating assay

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
B. Chemistry, Manufacturing, and Controls
2. End-of-Phase 3 Clinical Studies and Pre-NDA Considerations
g. Stability-indicating analytical methods

page 30, ¶ g.

"The stability of a botanical drug substance or product generally should not be based entirely on the assay of the active constituents, assay of the characteristic markers, or biological assay, because degradants formed during storage from other chemical constituents in the botanical drug substance or product should also be controlled."

The Guideline recommends developing an analytical method capable of detecting degradants produced by subjecting the Botanical Drug Substance and Botanical Drug Product to stress conditions. The degradants resulting from forced degradation of botanical materials are likely to be very complex and difficult to interpret. For example the composition of many botanical products will include active constituents and/or marker compounds as well as primary metabolites such as carbohydrates, amino acids and fatty acids. Forced degradations studies on this type of botanical mixture will yield complex, chemically diverse degradation products, which will be difficult to detect with one analytical method. Likewise, a chromatographic fingerprint would require comparison of complex peak patterns and quantitative determination of the amount of degradation at each stability time point. It is our opinion that the stability program for botanical products will be highly dependent on the nature of the botanical product. For this reason we recommend flexibility in defining stability requirements and that each program be negotiated with the agency, on a case-by-case basis.

4.3 Manufactured in accordance with drug CGMPs

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
B. Chemistry, Manufacturing, and Controls
2. End-of-Phase 3 Clinical Studies and Pre-NDA Considerations
i. *CGMPs* as set forth in 21 CFR Parts 210 and 211

page 31, ¶ i.

"The manufacturing and testing facilities for the drug substance and drug product should be ready for FDA inspection to determine if they are in conformance with CGMPs as set forth in 21 CFR Parts 210 and 211."

The "Draft ICH Consensus Guideline on Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" contains a table on page 3 entitled "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients". The purpose of the table is to indicate where, during the manufacturing process, the ICH GMP Guideline applies. One specific example is the manufacture of an herbal extract to be used as an active pharmaceutical ingredient. The ICH GMP Guideline states that plant harvesting, plant cutting and initial extraction are not governed by the GMP guideline, implying that GMP is not required for these steps. This appears to be in conflict with the FDA's Botanical Guideline, which requires GMP compliance for manufacturing facilities for the botanical extract. We would like clarification of this point.

4.4 Environmental Impact Analysis

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
B. Chemistry, Manufacturing, and Controls
2. End-of-Phase 3 Clinical Studies and Pre-NDA Considerations
j. EA

page 31, ¶ j.

"The Agency regards the submission of an NDA for a drug derived from plants taken from the wild as an extraordinary circumstance requiring the submission of an EA."

If crude extracts, derived from wild plants, are purchased from commercially available sources and used as the starting material for further processing into a Botanical Drug Substance will an EA still be required? Some plants, already in commerce for dietary supplements or Traditional Chinese Medicines, exist in their natural habitat on private lands (Saw Palmetto, for example). These lands are maintained to keep the plants in their natural state for commercial reasons and are not, technically, cultivated. Do these plants fall under the definition of "wild"?

5.0 PRECLINICAL SAFETY ASSESSMENT

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
C. Preclinical Safety Assessment (including Pre-NDA)

page 32, 1st full ¶

1. Repeated-Dose General Toxicity Studies

"If possible, the drug should be tested using the same formulation and route of administration as proposed for clinical use."

Please clarify the use of the term "formulation". Toxicology studies are usually conducted with drug substance, not the final product formulation. Does "formulation" refer to the manufacturing process used for the extraction of the botanical drug substance?

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